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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary

Application No.	Applicant(s)
09/745,506	Lal et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication..
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *23-41 and 43* is/are pending in the application.

4a) Of the above, claim(s) *23, 24, 34-38, and 40* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-33, 39, 41, and 43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Claim 42 has been canceled. Claims 25, 26, 30, 32, 39 and 41 have been amended. Claims 43 has been added. Claims 23, 24, 34-38 and 40 remain withdrawn from consideration. Claims 25-33, 39, 41 and 43 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. With regard to applicants comments on the restriction requirement it is noted that on page 2 of the prior Office action the examiner stated that "the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable".

4. The objection to claims 25-31 is withdrawn in light of applicants amendments. The objection to claims 27, 31 and 32 for reciting non-elected inventions is maintained for reasons of record. Applicant points out that according to as discussed in In re Weber, 198 USPQ (CCPA 1978) that it's applicants right, by statute to "to claim his invention with the limitations he regards as necessary to circumscribe that invention, with the proviso that the application comply with the requirements of 112". Applicant quotes Weber at 331 stating:

As a general proposition, an applicant has a right to have each claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed into a number of applications.....The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim.

This has been considered but not found persuasive. Firstly, the restriction requirement has been made final in the Office action of Paper no. 9. Until such time as a petition is considered by the PTO to reverse the examiners restriction requirement, the restriction requirement stands as

proper and must be adhered to. Secondly, the instant invention if separated into 37 separate applications each representing a single SEQ ID NO would indeed be the equivalent of the original claims, which were drawn to all of SEQ ID NO:1-37.

Appropriate correction is required.

5. Claims 25-33, 39 and 41 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility. New claim 43 is also rejected for the same reasons of record as set forth below.

The instant claims are drawn to the polynucleotide of SEQ ID NO:74 and the polynucleotides encoding SEQ ID NO:37. The instant application has provided a description of isolated polynucleotides encoding proteins and the proteins encoded thereby. The specification has collectively termed these proteins "NHRP". The instant application does not disclose the biological role for the NHRP protein of SEQ ID NO:37 or its significance. The instant specification asserts that it provides compositions which are useful in the diagnosis, prevention and treatment of diseases associated with cell proliferation, particularly immune responses and cancers (page 6, lines 1-4). The specification asserts that in cancers or immune disorders where NHRP is an "activator, transcription factor, enhancer, is being expressed, and is promoting cell proliferation; it is desirable to decrease the expression of NHRP" (page 44, lines 11-14). In cases where NHRP is an inhibitor or suppressor and not controlling cell proliferation it is desirable to provide the NHRP protein or increase the expression of NHRP (page 44, lines 14-16). The specification asserts that administration of NHRP of fragments thereof can be used to treat cancers such as "adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma", which include but are not limited to cancers of the "adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus" (page 44, lines 17-23). The specification asserts that

antagonist which decrease the activity of NHRP may be administered to prevent or treat "AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, Graves disease, hyper eosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections and trauma". The specification also asserts that administration of an antagonist of NHRP could treat or prevent cancers such as "adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma and particularly cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus" (page 44 line 29 to page 45 line 22).

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the NHRP proteins, or the specific NHRP protein of SEQ ID NO:37. The disclosed protein of SEQ ID NO:37 is purported to have a potential function based upon the association of the polynucleotide with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses (page 32, lines 24-30). After further research, a specific and substantial credible utility might be found for the claimed isolated polynucleotides. This further characterization, however, is part of the act of invention and until it has been undertaken the claimed invention is incomplete.

The specification states that the polynucleotides encoding the NHRP of the instant invention may be used for the diagnosis of conditions or diseases which are associated with expression of NHRP such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma,

sarcoma, and teratocarcinoma and cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and immune disorders such as AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, Graves disease, hyper eosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and thyroiditis (page 56, lines 2-15).

In order for a polynucleotide to be useful for diagnosis of a disease, as asserted, there must be a well-established or disclosed correlation between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in inflamed tissues or in tissues derived from cancerous cells is not sufficient for establishing a utility for the diagnosis of disease absent information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern or evidence of altered form that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know that the claimed polynucleotide is either present only in diseased tissue to the exclusion of normal tissue, or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained in an effort to

establish a differential expression pattern would constitute further research on the polynucleotide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696.

The instant claims are drawn to a protein of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that SEQ ID NO:37 or the polynucleotides encoding SEQ ID NO:37 of the instant application was, as of the filing date, useful for diagnosis, prevention and treatment of cell proliferation or immune response disorders or cancers, as stated above. Until some actual and specific significance can be attributed to the protein identified in the specification as SEQ ID NO:37, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

6. Claims 25-33, 39 and 41 are also rejected under 35 U.S.C. 112, first paragraph. New claim 43 is also rejected for the same reasons of record. Specifically, since the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

7. Applicant has submitted the Bedilion Declaration in order to provide persuasive evidence that the instant invention possesses patentable utility. Applicant argues that the Bedillion Declaration describes some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Applicant states that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing

drugs and monitoring their activity. Applicant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO:74 would be a more useful tool than microarrays lacking the same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and developmental disorders for such purposes as evaluating their efficacy and toxicity. This is not found to be persuasive. It is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party in interest in this appeal, and thus is a concerned party. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. Also, the assertion that the claimed inventions "uses", as opposed to its function, is the subject of a proper analysis under the utility requirement, does render the asserted utility specific, since the specification has not establishes that the NHRP of SEQ ID NO:37, or the encoding polynucleotide of SEQ ID NO:74 is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that NHRP is expressed in at altered levels or forms in tissues exhibiting a pathological state. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases states which correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is also not substantial.

Applicant argues that the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function is without merit. However, Applicant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, in the case of a hypothetical specification disclosing that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. ∞ 101 and 112, first paragraph, as it has utility

and is enabled as a colon cancer marker without the disclosure of the biological activity of the polypeptide encoded by the polynucleotide. However, such is not the fact pattern here. As stated in the previous Office action "The presence of a polynucleotide in inflamed tissues or in tissues derived from cancer cells is not sufficient for establishing a utility for the diagnosis of disease absent information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know that the claimed polynucleotide is either present only in diseased tissue to the exclusion of normal tissue, or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained in an effort to establish a differential expression pattern would constitute further research on the polynucleotide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696."

The instant specification discloses that the claimed polynucleotides encode SEQ ID NO:37 which is a human regulatory protein (page 17, line 19) which is related by sequence homology to a S cerevisiae protein sequence: GI 1322869. It is noted that neither the specification or any art of record has identified a specific and substantial utility, function or biological significance of said S cerevisae protein. On the basis of the observation that the claimed polynucleotides can be found in inflamed or cancerous tissues, the specification hypothesizes that the claimed polynucleotides are involved in the cancerous or inflamed states, but the expression of the polynucleotides or

polypeptide encoded therefrom in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. There is no disclosure of a specific gene which is regulated by the polynucleotides or polypeptide of the NHRP of the instant invention. It is noted that the instant application is claiming a priority date of June 6, 1997 No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue, or a gene which is regulated by the instant NHRP. Also, no evidence has been brought forth that the claimed polynucleotides encode polypeptides having a specific human regulatory activity.

Applicants argue at pages 13-17 of the response that the use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Applicant states that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicant asserts that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor; because these methods can be carried out with any orphan receptor the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Applicant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose

the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Applicant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of cell proliferative and developmental. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific cell proliferative or developmental disorder. The specification merely discloses that the claimed polynucleotides are predicted to encode a protein which has sequence homolog to a S cerevisiae protein, and that they are expected to be involved in cancerous and inflammatory processes. The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology.

Beginning on the first paragraph of page 14 of the response, Applicant refers to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a useful tool in connection with conducting gene expression monitoring studies in connection with the development of new drugs for the treatment of immune responses and cancers, and that a person skilled in the art would request specifically that any DNA microarrray being used for such purposes would contain the polynucleotide of SEQ ID NO:74. Again, this is not found to be persuasive, because the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. The examiner does not contest the fact that DNA microarrays have utility as a

laboratory method. DNA microarrays consist of numerous DNA probes, anchored at defined positions within a two-dimensional grid. These microarrays are used to screen for the presence or absence of a multitude of target polynucleotides in a single assay, and thus, DNA microarrays have utility for the collection of large amounts of experimental hybridization data in a short amount of time. The Applicantss are incorrect in assuming that placement of an uncharacterized polynucleotide within a DNA microarray conveys the utility of the laboratory method to the individual piece of DNA. This asserted "utility" is not specific to the claimed polynucleotides, as any DNA can be placed into the microarray in order to carry out further research into the expression of said DNA. Even if expression of Applicantss' claimed polynucleotide is altered by a test drug and is detected in a microarray for drug screening, the specification does not disclose any interpretation for the result. The Declaration fails to address the fact that information gained by the use of the claimed polynucleotides within a DNA microarray constitutes the experimentation needed in order to discover a patentable "real-world" utility for the claimed polynucleotides.. Further, the statement that one of skill in the art would have "specifically requested" the polynucleotide of SEQ ID NO:74 to be contained within an array" is not persuasive. The presence of the claimed polynucleotide in a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. °101.

In the middle of page 14 of the response, Applicant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Applicant points to Dr. Bedilion's pages of text and numerous sub-parts explaining the importance of this technology. Applicant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the

importance of toxicity testing. This is not found to be persuasive. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

In the second paragraph of page 15 of the response, Applicant argues that the examiner does not address the fact that, as described on pages. 14, 56, 58-59 and 67-68 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Applicant concludes that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it and this can be said for any polynucleotide. Thus, this asserted utility is not specific.

At page 15, third paragraph of the response, Applicant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Applicant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed

polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

On page 16 of the response, applicant refers to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522). Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. This is not found to be persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph.

Applicant refers to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology testing at pp. 16-17 of the response. Applicant specifically sites Rockett et al (Xenobiotica, 1999, vol. 29, pp. 655-691) who state that new pharmacological agents can be screened by microarrays comprising genes whose function are unknown. Rockett et al teach that new drugs can be compared to drugs with known function and efficacy using said microarrays, and new drugs yielding expression patterns that are similar to know drugs can then be selected for further testing (abstract, lines 4-7, and page 656, lines 23-35). Thus, Rockett et al teach that a microarray need not comprise genes having known function. However, this does not impart a patentable utility to the instant polynucleotide, as any orphan gene can be used in the microarrays described by Rockett et al.. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is

not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is a not substantial.

Beginning at p. 17 of the response, Applicant argues that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease, and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Applicant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at the bottom of page 18 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to

perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to drug discovery and development, Applicant asserts expression profiling as one use of the claimed polynucleotide. Applicant refers to recent developments, on page 19 of the response as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Applicant is incorrect in assuming that discoveries made using other genes, versus the instant polynucleotides, influence the patentability of the claimed polynucleotides.

Applicants argue on page 20 of the response, that commercial success derived from the sale of polynucleotides databases comprising expressed genes lends credence to the assertion that the instant polynucleotides add "more than incremental benefit to the drug discovery and development process" Applicant argues that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest in the instant appeal. Applicant urges that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Applicant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. ° 101 for lack of operability can be overcome by a showing of actual use or commercial success. The instant issue is not lack of operability but whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.. Furthermore, although the sale of a newly identified cDNA to other researchers who would then attempt to elaborate a functional use for any potential encoded protein may be lucrative, it is the responsibility of the applicants, not the purchaser, who must disclose the

specific use of the protein in order to satisfy the requirements of patent law. For these reasons, utility cannot be equated to commercial success.

Applicant argues on page 20 that the examiners rejections are without merit as a matter of law and of fact. The essential disagreement seems to be that the asserted utilities for the claimed polynucleotides are not specific, substantial and credible.

Applicant argues on page 20, that the precise biological significance or function of an expressed polynucleotide is not required to demonstrate utility. The examiner agrees that in cases where an empirical association between a polypeptide or polynucleotide and a disease state is set forth, it would not be necessary to demonstrate a precise biological role for the protein. Also in the event that the protein would have a well-established utility, such as a ligase, it would not be necessary to set forth an additional utility. However, for the reasons set forth above, the claimed polynucleotides or polypeptides encoded therefrom have neither specific correlation to a disease state or well-established utility. Applicant states on page 14, lines 4-7 that "It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States Patent". The examiner agrees with this analysis. However, as the specification is lacking any empirical correlation with a disease state or a well-established utility for the claimed polynucleotides or polypeptide encoded thereby, the instant specification does not fulfill the requirement for a United States Patent. Furthermore, not all disclosures in technical journals necessarily fulfill the requirements of "real world" utility. Applicant cites the USPTO utility guidelines and quote "The utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has gene regulating activity". In the absence of a specific function for the encoded product, a empirical correlation with a disease state would be adequate to establish patentable utility. The

specification has provided neither a specific association with a disease state nor a specific gene or receptor which is regulated by the encoded proteins.

At page. 22 of the response, Applicant argues that the utility of the claimed polynucleotide can be imputed based on "membership in a class of useful products". Applicant argues that as long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility. This has been considered but not found persuasive. In order to satisfy the utility requirement it is necessary for a specific, substantial and credible utility to be disclosed. Obtaining a U.S. patent is not based on a statistical probability of utility. Further, the specification has not asserted an art recognized class of compounds to which the disclosed polypeptides would belong. Instead applicants argue that the disclosed polypeptides belong to the class of "expressed polynucleotides" which has been pre-selected by nature to be useful (bottom of page 22), this has been considered but not found to be persuasive. In order to obtain a U.S. patent, it is applicant's responsibility to determine the specific, substantial and credible use that was pre-selected by nature. Applicant further argues that the demonstration that the claimed polynucleotide encodes a polypeptide that is expressed by humans is more than sufficient to make it useful for the diagnosis and treatment of diseases associated with cell proliferation, particularly immune responses and cancers. Applicant states that NHRP-1 has been shown to be expressed in cDNA libraries associated with cancer or inflammation and that the examiner must accept these facts or provide sound scientific reasoning to the contrary. This has been considered but not found persuasive. The examiner has not challenged the fact that the claimed polynucleotides can be found in libraries associated with cancer and inflammation. The examiner is challenging the lack of evidence that the claimed polynucleotides are indicative of a pathological state such as cancer or inflammation. actin and histone genes are expressed in diseased tissues, but as they are constitutively expressed in all tissues, they are not indicative of a specific pathological state.

Applicant agues on page 23 of the response, that because the uses of the claimed polynucleotides include toxicology testing, drug discovery and disease diagnosis which are practical uses beyond mere study of the polynucleotide itself, the claimed invention has substantial utility. For the reasons stated above, the instant specification has provided no disclosure on the use of the claimed polynucleotides in disease diagnosis. Using the claimed polynucleotides in a panel or array of polynucleotides to obtain a pattern of changes resulting from xenobiotics of unknown function, as proposed by Rockett et al, does not impart a specific, substantial and credible utility to the claimed polynucleotide as any orphan polynucleotide can be used for such purpose.. Applicant argues that the claimed polynucleotides would be useful in chromosomal mapping. However, as stated above, any expressed polynucleotide can be used to hybridize to a chromosome, and therefore this utility is not specific to the instant expressed polynucleotide. If, however, the claimed polynucleotides had been disclosed as mapping to a chromosomal location associated with a specific disease state such as a chromosomal breakpoint associated with leukemia, or a chromosomal locus which was amplified in specific cancers, and the specification asserted that the claimed polynucleotides could have been used as a chromosomal probe related to said cancers, such would have been accepted as a patentable utility even though it is unrelated to the function of the polypeptides encoded by the claimed polynucleotides.

Applicant agues on page 24 that differential expression associated with a disease state is irrelevant to toxicology testing. Applicant continues to allege that the claimed polynucleotides can be useful for toxicology testing in drug discovery without any knowledge of differential expression or disease association. Clearly any expressed polynucleotide can be used in the "open system" as set forth by Rockett et al as the first generation screen for patterns of gene changes based on exposure to a xenobiotic (Rockett et al page 656, lines 23-35). The technique describe by Rockett does not impart patentable utility to the claimed polynucleotides because it can be preformed with any polynucleotides. Therefore, it is not specific to the instant polynucleotides.

On pages 24-26 applicant interpreted the utility guidelines. Applicants state that although the utility guidelines prohibit a "throwaway" utility, they do not preclude a "general" utility. Applicant admits that this is contrary to what has been set forth in the training materials which expressly require a specific and substantial utility. Applicant concludes that the training materials are inconsistent with the law. This issue will not be addressed because an Examiner has no authority or specific knowledge to comment on the legality of the Guidelines.

Applicant argues on page 26 that the rejection under 35 U.S.C. 112, first for lacking utility must be reversed, as the utility rejection is improper. This is not persuasive as the utility rejection is maintained for reasons of record.

8. In the event that applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to polynucleotides that encode SEQ ID NO:37; polynucleotides comprising SEQ ID NO:74, the complete complement of SEQ ID NO:74, an isolated polynucleotide consisting of a fragment of the complement of SEQ ID NO:74,; and an array comprising a polynucleotide complementary to SEQ ID NO:74, wherein said polynucleotide is completely complementary to SEQ ID NO:74; because the specification does not reasonably provide enablement for polynucleotides that encode a fragment of SEQ ID NO:37, polynucleotides encoding polypeptides having at least 95% identity to SEQ ID NO:37, polynucleotides comprising naturally occurring polynucleotides having at least 95% sequence identity to SEQ ID NO:74, an isolated polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:74, polynucleotides at least 95% identical to SEQ ID NO:74; micorarrays or arrays comprising SEQ ID NO:74 or microarrays or arrays comprising polynucleotides at least 95% identical to SEQ ID NO:74. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A) As drawn to polynucleotides encoding a polypeptide comprising an amino acid sequence at least 95% identical to SEQ ID NO:37 and polynucleotides comprising a polynucleotide sequence at least 95% identical to SEQ ID NO:74

Claims 25, 28-30, 32, 33, 39, 41 and 43 encompass polynucleotides comprising non-disclosed nucleic acid sequences, that is polynucleotide variants of SEQ ID NO:74, polynucleotides which encode variant polypeptide of SEQ ID NO:37, and polynucleotides having 95% sequence identity to SEQ ID NO:74. The specification does not teach polynucleotides encoding a naturally occurring polypeptide having 95% identity to SEQ ID NO:37 or naturally occurring polynucleotides having 95% identity to SEQ ID NO:74. The specification states that alleles result from at least one mutation in the nucleic acid sequence and may result in mRNAs or polypeptides whose structure or function may or may not be defined (page 10, lines 1-4). The specification states that altered nucleic acid sequences encoding NHRP include those with deletions, substitutions or insertions of different nucleotides that result in a polynucleotide that encodes the same functionally equivalent NHRP (page 10, lines 8-10). However, the specification also states that variants of NHRP include amino acid sequences having non-conservative changes in the amino acid sequence (page 17, lines 11-12).

The claims are broadly drawn to variant polynucleotides and polynucleotides encoding variant polypeptides. The specification neither limits nor defines naturally occurring polynucleotide having 95% identity to SEQ ID NO:74 or naturally occurring amino acid sequences having 95% identity to SEQ ID NO:37. The specification neither limits nor defines fragments of the amino acid sequence of SEQ ID NO:37 for the reasons set forth in the rejection under 112, second paragraph, below. Further, the variants as defined in the specification include but are not limited to allelic sequences, altered NHRP and variants of NHRP. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a large species of polynucleotides that encode numerous proteins having neither structural nor functional identity with polynucleotides encoding SEQ ID NO:37 and no guidance has been given as to how to use

these species. The specification has not shown that polynucleotides encoding polypeptides comprising variants of SEQ ID NO:37 or polynucleotide variants of SEQ ID NO:74 are capable of functioning as polynucleotides encoding SEQ ID NO:37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use the polynucleotides that encode the broadly claimed polypeptides. The relationship between amino acid sequence and protein function is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (Journal of Cell Biology, 1990, Vol. 111, pp.2129-2138) replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (page 2132 column 1 to page 2133 column 2). In the case of TGF alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the altered TGF alpha. (Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252, page 1250 bridging paragraph). These references demonstrate that even a single amino acid substitution or what appears to be a minor modification will often dramatically affect the biological activity of a protein. Clearly, it could not be predicted that a variant polynucleotide, or polynucleotide encoding a variant protein would have equivalent functional characteristic of the polynucleotide which encodes SEQ ID NO:37. Further, one of skill in the art would not be able to screen variant polypeptides based on functional characteristic because the specification has not disclosed any regulatory, structural of biochemical characteristic of SEQ ID NO:37. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variant polynucleotides, or polynucleotides encoding variant proteins.

Claim 33 is drawn to an isolated polypeptide which comprises 60 contiguous nucleotides of SEQ ID NO:74, the complementary sequences thereof, or a naturally occurring polynucleotide

having 95% sequence identity to SEQ ID NO:74 or the complementary sequences thereof. It is noted that claim 33 encompasses both sense and anti-sense strands of SEQ ID NO:74 and the naturally occurring variant of SEQ ID NO:74, however the specification does not teach how to use a probe comprising a sense strand of SEQ ID NO:74 or a sense strand of a naturally occurring variant of SEQ ID NO:74. Aforesaid probes would hybridize to genomic DNA, and there are no teachings in the specification or any art of record to support the notion that binding of a probe to genomic DNA would be diagnostic for the diseases and conditions recited on page 56, lines 2-15, as the recited disorders are asserted to be associated with aberrant NHRP expression in contrast to the presence of the gene in the genome. Thus, it can be concluded that the specification does not teach a use for a polynucleotide probe comprising at least 60 contiguous nucleotide residues of SEQ ID NO:74, or a naturally occurring variant of SEQ ID NO:74.

Furthermore, claim 33 is drawn to isolated polypeptides which comprise, rather than consist of, 60 contiguous nucleotides of SEQ ID NO:74 or a variant of SEQ ID NO:74, or the complements of either of the aforesaid polynucleotides. Given the broadest reasonable interpretation, the claim reads on a large genus of polynucleotides in excess of 60 nucleotides and the specification has not a use for the broadly claimed polynucleotides. The specification has not taught that a polynucleotide sequence comprising 60 contiguous nucleotides of SEQ ID NO:74 in addition to non-disclosed nucleotides would serve as a diagnostic indicator for the same disease states as SEQ ID NO:74. The specification has not taught that transferring 60 contiguous nucleotide of SEQ ID NO:74 into a longer polynucleotide sequence would result in polynucleotide encoding a polypeptide having the same functional characteristic of SEQ ID NO:37. It is well known in the art that proteins are folded three-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry (text), 1996, pp. 165-171). In any given protein amino acids distant from one another in the primary sequence may be closely located in the folded three-dimensional structure. (Mathews and Van Holde, figure 6.1). The specific conformation of a protein results

from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the NHRP of SEQ ID NO:37 protein can potentially radically alter the three dimensional structural environment in which the given fragment is located (Matthews in Perspectives in Biochemistry, 1989, Ed. H. Neurath, pp. 6-9, page 6, second column, first paragraph) and the consequences of the altered sequence environment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects must be considered with respect to protein function in addition to molecular aspects (Bork, Genome Research, 2000, vol. 10, pp. 398-400, p. 398, column 2, first paragraph). Furthermore, it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims would not share functional properties with the polynucleotides of SEQ ID NO:74 or encode proteins that share functional properties of SEQ ID NO:37. The function of the claimed polynucleotides cannot be predicted, and has not been taught by the specification. Thus, with the exception of a polynucleotide sequence consisting of 60 contiguous amino acid sequence of the complete complement of SEQ ID NO:74, one of skill in the art would be forced into undue experimentation in order to use the broadly claimed polynucleotides..

(B) An array comprising: SEQ ID NO:74, an array comprising a polynucleotide having at least 95% sequence identity to SEQ ID NO:74, an array comprising the complete complement of a polynucleotide having at least 95% sequence identity to SEQ ID NO:74

Claims 39 and 41 are drawn to arrays comprising fragments of the polynucleotides of claim 32 and 33. It is noted that the polynucleotides encompass both sense and anti-sense strands of SEQ ID NO:74 and variants of SEQ ID NO:74, and for the reasons states above, the specification is not enabling for probes consisting of the sense strand of SEQ ID NO:74 or a variant of SEQ ID NO:74 as the probe would hybridize to genomic DNA. Further, the specification is not enabling for probes comprising fragments of the anti-sense strand of the variant of SEQ ID NO:74 as the specification has not taught how to use all the possible variants

of SEQ ID NO:74 as stated in the rejection above, regarding naturally occurring polynucleotides having at least 95% sequence identity to SEQ ID NO:74. For these reasons, one of skill in the art would not know how to use the broadly claimed arrays for the detection of the diseases stated on page 56, lines 2-15.

(C) As drawn to polynucleotides encoding fragments of SEQ ID NO:37

Claim 25 is drawn in part to polynucleotides encoding immunogenic fragments of SEQ ID NO:37.. Claim 25 is also drawn in part to immunologically active fragments of SEQ ID NO:37.. The specification states that antibodies which specifically bind NHRP may be used for the diagnosis and conditions or diseases characterized by expression of NHRP, or in assays to monitor patients being treated with NHRP, agonists, antagonists or inhibitors (page 54, lines 17-19). Further, the specification has not provided teachings for how to use any antibody generated to peptides of SEQ ID NO:37. The specification contemplates the administration of antibodies which specifically bind NHRP may be used directly as an antagonist or may be used indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express NHRP. The specification has not taught how to make antibodies which antagonize the action of the NHRP of SEQ ID NO:37 as the specification has not taught a receptor or a ligand for NHRP. The specification has not taught if NHRP is expressed on the cell surface as an antigenic target, or if NHRP is involved in signal transduction within the cytosol, or if NHRP binds directly or indirectly to nuclear DNA. Without a specific function attributable to the NHRP of SEQ ID NO:37 one would not know if an antibody which bound to SEQ ID NO:37 was able to antagonize said function or inhibit a putative binding with a ligand or receptor. Further, with regard to the delivery of a pharmaceutical to a disease site, the specification does not teach that SEQ ID NO:37 is accessible on the cell surface. Given this lack of teaching, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the broadly claimed fragments of SEQ ID NO:37.

The specification provides insufficient guidance with regard to all of the issues above and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention.

Applicant argues on pages 27-29 that the specification discloses how to make and use the claimed variants, fragments and mRNA equivalents. This has been considered but not found persuasive. The cited portions if the specification describe only general methods of manipulating recombinant polynucleotides and chemically synthesizing fragments of the claimed polynucleotides. Because the specification has not provided a specific use or function for the claimed polynucleotides, the claimed variants, fragments and mRNA equivalents cannot be limited by a specific use or function and potential include polynucleotides having alternative uses or functions, beyond those yet not be established for SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37 which are not set forth in the specification. Applicant argues on the top of page 29 that it would not be undue experimentation to use a polynucleotide encoding an immunogenic fragment of SEQ ID NO:37 because only antibody binding need be tested. This has been considered but not found persuasive. The generation of an antibody or an immunogen-antibody complex cannot be regarded as enablement for "how to use" the immunogenic fragment. Because the specification has not defined a specific disease or condition related to the instant polynucleotides, one of skill in the art would not know how to use antibody resulting from the immunogenic fragment for detection or diagnosis of a disease. One of skill int eh art would not know how to use a the instant polynucleotides encoding the immunogenic fragment for a preparation of a vaccine against a specific disease or condition as said disease or condition has not been identified. Applicant argues that the references of burgess et al, Lazar et al, Mathews and Va Holde, Mathews and Bork do not support the examiners position that the claimed variant structures may have different biological functions than SEQ ID NO:74 and 37. Applicant again argues that all of the variants and fragments claimed are enabled by virtue of the fact that they are

expressed polynucleotides, and additionally able to be used in toxicology testing. Applicant states that the examiner has confused use with biological function. This has been considered but not found persuasive. For the reasons states above, a expressed polynucleotide does not have a specific utility by virtue of its being an expressed polynucleotide or being included in a microarray. The examiner has not confused use with function, however, the disclosure enables neither use not function for the disclosed polynucleotide of SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37.

9. The rejection of claims 25, 28, 29, 30, 32, 33, 39, and 41 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. The rejection of newly added claim 43 is made for the same reasons.

Applicant has amended the claims to recite a 95% sequence identity in place of a 90% sequence identity. However, the rejection was made on the basis of the limitation of "naturally occurring" which was not contemplated by the specification or claims as originally filed as a limitation for the claimed variants. It is noted that claim 33 persists in incorporating the limitation of 60 consecutive nucleotides of claim 32, although page 17, lines 14-17 state that the new limitation of "60 consecutive nucleotides" was not contemplated in the specification or claims as originally filed. .

The specification contemplates allelic sequences on page 10, lines 1-7, and NHRP variants having 90% sequence identity the NHRP sequence, however, this is not adequate basis for naturally occurring amino acid sequences having at least 90% identity to SEQ ID NO:37 or naturally occurring polynucleotide sequences having 90% sequence identity to SEQ ID NO:74. The specification or originally filed claims did not contemplate arrays comprising oligonucleotides complementary to polynucleotide having 95% identity to SEQ ID NO:74.

Because of the introduction of new matter, one of skill in the art would not be reasonablely assured that applicant had possession of the claimed invention at the time of filing.

10. The rejection of claims 25, 28, 29, 30, 32, 33, 39 and 41 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. The rejection of new claim 43 is made for the same reasons.. Claim 25 is drawn in part to polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to SEQ ID NO:37 Claim 28 specifically embodies the polynucleotide of claim 25 wherein a promoter is operably linked to said polynucleotide. Claim 29 specifically embodies a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn in part to methods of producing polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to SEQ ID NO:37 Claim 32 is drawn in part to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to SEQ ID NO:37, and a complement thereof.

The written description in this case only sets forth polynucleotides encoding SEQ ID NO:37, polynucleotides comprising SEQ ID NO:74, and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acids sequences having 95% sequence identity to SEQ ID NO:37 or polynucleotides comprising a naturally occurring polynucleotide sequences at least 95% identical to SEQ ID NO:74,

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. (See page 1117). The specification does not clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The claims are drawn to a genus of variant polynucleotides and neither the common attributes of the genus nor specific examples of species representative of the genus have been described. The structures of naturally occurring polynucleotides having 95% sequence identity to SEQ ID NO:74 and polynucleotides encoding polypeptide having 95% sequence identity to SEQ ID NO:37 are not defined by structure or function and cannot be anticipated from the art.

With the exception of SEQ ID NO:74, and the polynucleotides encoding SEQ ID NO:37, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

For the reasons set forth above, the specification is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

11. Applicant argues on page 31 of the response that the statement in the originally filed application that "a naturally occurring expressed polynucleotide sequence at least 95% identical to a expressed polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74" satisfy the written description requirement regarding the possession of the genus of polynucleotides. This is not persuasive. Examination of the specification and the originally filed claims 1-21 indicates that the statement "a naturally occurring expressed polynucleotide sequence

at least 95% identical to a expressed polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74" was absent. The quotation supplied by applicant on page 31 that "Thus, the invention contemplates each and every possible variation of nucleotide sequence that could be made in accordance with the standard triplet genetic code as applied to nucleotide sequence of naturally occurring NHRP, and all such variations are to be considered as being specifically disclosed." Clearly the specification contemplated all expressed polynucleotide sequences encoding SEQ ID NO:37 due to the degenerate genetic code. However, the statement of "all such variations" does not provide support for naturally occurring variants having 95% homology to SEQ ID NO:74 or polynucleotides encoding SEQ ID NO:37. It is noted that the quoted statement did not apply the adjective "naturally occurring" to the variants, and further, a specific sequence homology was not suggested. However, even in the event that the statement of naturally occurring expressed polynucleotide sequence at least 95% identical to a expressed polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74 was present in the application as filed this does not entitle applicant to the possession of the genus. Applicant argues that the specification describes variant of SEQ ID NO:37 on page 17, lines 8-16 and page 33, lines 1-5. The textual citation referenced by applicant are only a general discussion of a variant, no specific sequences are described. Applicant alleges that the chemical and structural features of NHRP are described on page 32, lines 24-30. This citation describes only potential glycosylation sites and potential phosphorylation sites within SEQ ID NO:37, the specification does not address the conservation of said glycosylation or phosphorylation sites with the claimed variants or fragments. Applicant argues that one of skill in the art would know how to use the BLAST program to determine 95% identity. That argument is moot because the requirement for written description is not whether one of skill in the art would know how to make and use, but if applicant sufficiently described the claimed invention. Applicant seems to confuse the contemplation of the genus of variants and the genus of polynucleotides encoding fragments and the genus of undefined RNA equivalents with the actual possession of the genus and continually

places emphasis on "whatever is now claimed" as stated in Vas-Cath, Inc v Mahurkar (page 31 of the response). The examiner believes that the rejection was on claims which are under consideration, and therefore was indeed what was now claimed. Further, as stated on page 19 of the previous Office action "Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.". Thus, the contemplation of the aforesaid genuses does not constitute an adequate written description.

Applicant argues on page 37 that the instant case differs from previous cases such as Lilly and Fiers because the there is no reliance on a description or functional characteristic of the polypeptides recited in the claims because the instant claims recite structural features. This is not persuasive, the instant claims do not recite structural features, they recite only sequence homology. This is not the same a structural feature such as a catalytic site or a binding site. Further, the discussion on page 32, lines 24-30 of the predicted glycosylation and phosphorylation sits within SEQ ID NO:37 cannot be construed as to a limitation for the variants and fragments of the encoded polypeptides. Furthermore, no where in the specification or claims as filed, is it stated that the claimed variants or fragments must preserve the glycoslyation sites and phosphorylation sites. Thus, the instant genus claims are not limited by structural features.

Applicant argues on page 37 that Brenner et al have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues and that local identity is particularly important in this case for assessing the significance of the alignment. Applicant states that Brenner et al further report that greater or equal to 40% identity over at least 70 residues is reliable in signifying homology between proteins. Applicants reliance of Brenner et al is misplaced as Brenner et al is teaching the identification of evolutionary relationships which differs significantly from a functional relationship or a relation of common use. Further, the citation on page 6076 states that "we learn that 30% identity is a

reliable threshold for this database only for sequence alignments of at least 150 residues". On page 6073, second column third full paragraph the database is defined as the "structural Classification of Proteins database which is derived from structural and functional characteristics" . Thus, Brenner is predicting evolutionary relationships within a database of orthologs which are identified independently of sequence comparison. The instant genuses are not limited by functional attributes for the reason set forth above. Thus, reliance on %90 or %95 sequence identity does not guarantee that the variants will have the same functional attributes as SEQ ID NO:37. Further, Brenner et al teach on page 6074, bridging paragraph, that the comparison of structures is more powerful than the comparison of sequences. And that if two proteins show a high degree of similarity in their structural details and function, it is very probable that they have an evolutionary relationship. It is clear that the "function" of a protein cannot be derived solely from sequence information, as recognized by Brenner.

Applicant argues that the state of the art at the time of the present application is further advances than at the time of Lilly and Fiers. This argument is no applicable to the written description requirement because conception is not achieved until reduction to practice has occurred regardless of the ease of isolation of the claimed polynucleotides. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Applicant argues that there is simply no requirement that the claims recite particular variant and fragment polypeptide or expressed polynucleotide sequences because the claims already provide sufficient structural definition in claimed subject matter (page 34, second paragraph of the response). This has been considered but not found persuasive. Neither the specification nor claims identify common attributes shared by members of the genus in terms of use or function. Accordingly any expressed polynucleotide having 95% sequence identity to the

polynucleotides encoding SEQ ID NO:37 or the expressed polynucleotide of SEQ ID NO:74 would be a member of the genus. Thus the genus is highly varied as it includes polynucleotides having no relationship in terms of function or use to the instant SEQ ID NO:74. Therefore, SEQ ID NO:74 or the expressed polynucleotide encoding SEQ ID NO:37 fails to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus. Thus, applicant was not in possession of the claimed genus.

12. The rejection of claims 25-33, 39 and 41 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of applicants amendments.

13. The rejection of claim 32 under 35 U.S.C. 102(b) as being anticipated by the New England Biolabs Catalog, (1994, page 91) is withdraw in light of applicants amendments.

14. The provisional rejection of claims 25, 28, 29, 30, 32, 33, 39, 41 and 42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 7 of copending Application No. 09/539,800 is maintained. Acknowledgment is made of applicants intention to file a terminal disclaimer until such time as there is an indication of allowable subject matter.

New Grounds of Rejection

15. Claims 28 and 29 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. When given the broadest reasonable interpretation, claims 28 and 29 read on a recombinant polypeptide, or transformed cell comprised within an organism which does not exclude a human. Amendment of the claims to recite ---isolated

recombinant polynucleotide--- and ---an isolated cell--- would overcome this rejection. Please not that the dependence of claim 25 which recites "an isolated polynucleotide" does not impart the limitation of "isolated" to the recombinant expressed polynucleotide or transformed cell. The limitation is imparted only to the polynucleotide of claim 25 which is comprised within the cell or recombinant expressed polynucleotide. -

16. In the event that applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to isolated recombinant polynucleotides and isolated cells comprising said polynucleotides because the specification, while being enabling for the claimed recombinant polypeptide and cell which are not comprised within an organism, does not reasonably provide enablement for the claimed recombinant polynucleotide and cell which are comprised within an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification states on page 16, lie 28 to page 17, line 4 that transformation includes viral infection and particle bombardment. The specification states on page 37, line 27 to page 38, line 4 that expression vectors include viral expression vectors as well as animal cell systems. On page 39 lin 30 , to page 40, line 10 the specification contemplates that mammalian host cells wherein adenovirus is used as an expression system and the delivery of human artificial chromosomes for therapeutic purposes. When given broadest reasonable interpretation, the claims encompass recombinant vectors and transformed cells which are comprised within humans by means of gene therapy, or comprised within other organisms, such as transgenic animals. In either case the intended use falls into an art which is not well established or predictable.

(A)As drawn to a treansformed cell within a human or animal as a result of gene therapy

the instant specification does not teach how to overcome problems with in vivo delivery and expression. The state of the art as of the priority date of the instant application is that in vivo

gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82). The specification does not provide guidance to overcome these issues One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make the recombinant expressed polynucleotide or cell within an organism by means of gene therapy.

(B) as drawn to a transgenic animal

The specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing trangsgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287, see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genom, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would

undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

17. The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. For example see page 20, line 6, 16, , 27 and 28, page 21, lines 9, 19, 20, 30, page 22, lines 10, 11, 21, page 23, lines 2, 3, 14, 25, page 24, lines 6, 16, 17, 27, , page 25, line17, 27, , page 26, lines 7, 8, 18, 19, 29, page 27, lines 8, 17, 27 and 28, page 29, through to page 32. Appropriate correction is required.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

April 21, 2003.